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TITLE: A Phase II Immunotherapeutic Trial: Combination Androgen Ablative Therapy and CTLA-4 Blockade as a Treatment for Advanced Prostate Cancer

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14. ABSTRACT The objectives of this study are to generally test whether the addition of CTLA-4 blockade can enhance clinical treatment responses in advanced prostate cancer patients compared with treatment with AA therapy alone. Upon enrollment patients will be randomized to 3 months of concurrent AA therapy + MDX-010 or 3 months of initial AA therapy alone. At Mayo Rochester we have enrolled 14 patients. Of these, roughly 10 have sufficient follow-up to assess whether any treatment effects may be occurring: 5 patients have only received hormone therapy; 5 patients have received hormone therapy in combination with MDX-010. Thus far, those 5 patients who have received the combination of hormone therapy along with MDX-010 have generally demonstrated greater responses than patients that have received only hormone therapy alone. Specifically, the 5 test subjects have experienced faster declines in their PSA. This suggests that MDX-010 causes hormone therapy to work more effectively than using hormone therapy alone. Additionally, we have observed that some of the test subjects experienced a more prolonged response (diminished PSA) relative to those that received hormone therapy alone. Based on these preliminary observations, our strong hunch is that patients who received hormone therapy plus MDX-010 treatment may be deriving a benefit from the experimental form of therapy beyond that which occurs using standard treatment (which is hormone therapy alone).					
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## **Introduction**

This is an open-label, two-center, randomized phase II trial in which 108 patients with newly diagnosed advanced prostate cancer will be prospectively enrolled onto study. Patients with T3, N0, MX prostate cancer or patients with any T stage, N1 (defined as a single positive lymph node 2cm or less in size) and/or limited skeletal metastases will be considered for study inclusion. Limited skeletal metastases is defined as  $\leq 3$  metastatic lesions on bone scan. Patients must have undergone diagnosis and staging of their prostate cancer within 120 days of enrollment. Upon enrollment patients will be immediately randomized to receive either: i) 3 months of concurrent AA therapy + MDX-010 (treatment group) or ii) 3 months of initial AA therapy alone (control group). Fifty four patients will be randomized at the Mayo Clinic, while the remaining 54 patients will be randomized at the University of California-San Francisco Comprehensive Cancer Center. Equal numbers of control and treatment group patients will be enrolled onto study at these two institutions over a period of eighteen months.

## **Body**

On February 13, 2004, the Mayo Clinic received notification from the USAMRAA that Modification No. P00001 for Grant No. DAMD 17-02-1-0245 was fully executed.

On March 25, 2004, a site visit was conducted by Medarex at which time it was noted that the drug administration language in the protocol also needed to be revised; administration of the study drug was no longer feasible in the manner written in the protocol.

A protocol modification dated April 8, 2004 was approved by the Mayo IRB on May 20, 2004. The revised protocol was subsequently submitted to the USAMRMC office. At this time, even though the protocol was considered active and open to enrollment, we were unable to proceed with study enrollment until we could obtain approval of the April 8, 2004, amendment, due to the changes in the drug administration language that were required.

Additional documents were subsequently requested by the HSRRB, and a Memorandum for Record (dated August 18, 2004) was generated in response to the amendments which the USAMRMC office received on June 14, 2004, and the additional information which Dr. Beitins of the HSRRB received on July 12, 2004.

A site visit from the USAMRMC office took place at Mayo Clinic Rochester on November 19, 2004.

On December 20, 2004, the USAMRMC office sent the draft recommendations from the December 8, 2004 HSRRB meeting to Dr. Kwon.

On January 4, 2005, the official HSRRB review of the protocol (dated December 8, 2004) was sent to Mayo. On January 26, 2005, Mayo responded to the HSRRB meeting requests; a revised protocol and consent dated January 25, 2005 were submitted to the HSRRB. On January 27, 2005, Dr. Kwon received notification from Dr. Beitins of the HSRRB that the documents submitted on January 26, 2005, were approved by the Acting Chair of the HSRRB. The revised protocol and consent form

dated January 25, 2005, were subsequently approved by the Mayo IRB on February 24, 2005. An approval memorandum was issued to the Mayo contract specialist by Colonel Laura Brosch on March 15, 2005.

Recruitment activities commenced at Mayo in early April, 2005, and have been ongoing since that time. The determination has been made that we will need to be particularly aggressive with recruitment activities, and we have increased our efforts extensively. These recruitment efforts have consisted of:

- distributing printed flyers to staff urologists, residents, and physician assistants (PAs)
- posting study flyers on intra-clinic bulletin boards
- posting study flyers in all of the exam rooms
- sending weekly e-mail notifications to staff physicians, residents, and PAs
- scheduling individual one-on-one meetings with Dr. Kwon and the staff urologists
- presentations of the protocol at staff and resident meetings
- daily review of physician calendars for potential participants
- daily telephone calls to physicians, residents, and PAs each morning asking for referrals of any potential participants that they may see during the day
- networking with nurses, technicians, paramedical personnel, appointment schedulers, and other RN study coordinators within the Department of Urology

Dr. Kwon and the RN study coordinator have successfully established good working relationships with the staff urologists, residents, and PAs in the Department of Urology, and they plan to continue these recruitment activities. We will continue to identify additional recruitment tactics as well.

At Mayo Clinic Rochester we have enrolled 14 advanced prostate cancer patients in our study. Of these patients, roughly 10 have sufficient follow-up to assess whether any treatment effects may be occurring: 5 patients are regarded as "control" patients and have only received hormone therapy (removal of testosterone only, which is considered standard of care); 5 patients are considered "test" subjects and have received hormone therapy in combination with MDX-010 (an immune-boosting experimental agent that has been shown to promote cancer regression).

Thus far, those 5 patients who have received the combination of hormone therapy along with MDX-010 have generally demonstrated greater responses than patients that have received only hormone therapy alone. Specifically, the 5 test subjects have experienced faster declines in their PSA (prostate specific antigen) which is a blood marker that correlates with the extent of prostate cancer within their body. This suggests that MDX-010 causes hormone therapy to work more effectively than using hormone therapy alone.

Additionally, we have observed that some of the test subjects experienced a more prolonged response (diminished PSA) relative to those that received hormone therapy alone. Based on these preliminary observations, our strong hunch is that patients who received hormone therapy plus MDX-010 treatment (immune boosting) may be deriving a benefit from the experimental form of therapy beyond that which occurs using standard treatment (which is hormone therapy alone).

No patients have been enrolled to date at the University of California-San Francisco site.

### **Key Research Accomplishments**

- Protocol amendments approved by the DOD HSRRB and the Mayo IRB.
- Enrollment opened at Mayo Clinic Rochester.
- Fourteen study participants enrolled.

### **Reportable Outcomes**

No reportable outcomes have resulted from this research to date.

### **Conclusion**

Thus far, we have treated 14 advanced prostate cancer patients in our study. Of these patients, roughly 10 have sufficient follow-up to assess whether any treatment effects may be occurring. Five patients are regarded as "control" patients and have only received hormone therapy (removal of testosterone only, which is considered standard of care). Five patients are considered "test" subjects and have received hormone therapy in combination with MDX-010 (an immune boosting experimental agent that has been shown to promote cancer regression).

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Please see the attached table.

### **References**

No publications have resulted from this research to date.

### **Appendices**

Not applicable.

### **Supporting Data**

See attached table.

IRB #1564-02; MC0253 "A Phase II Immunotherapeutic Trial: Combination Androgen Ablation Therapy and CTLA-4 Blockade as Treatment for Advanced Prostate Cancer." Updated January 27, 2006

Initials	Study#	Study Arm	Disease Stage	Baseline PSA	Pre-tx PSA	PSA day 7 post MDX-010	Mo 1 PSA	Mo 2 PSA	Mo 3 PSA	Mo 4 PSA	Mo 5 PSA	Mo 6 PSA	PRE-MDX-010	Mo 7 PSA	Mo 8 PSA
GLE	12390	C	T3N1M0	5.8	7.7		0.54	<0.1	<0.1	0.36	2.5/4.1	5.9	11.1	Cross-over	
AAL	12848	T	T3N0M1	94.0	73.1	NA	7.5	1.6	0.8	0.58	9.6/13.1	Off/RRP			
MC	13011	C	T3N0M1	97.3	97.3		48.8	54.6 Off study RoRx & AA	72.6	52.2 at Mo 3.5	38.2	17.6			
MJA	98321	T	T3N0M0	136.5	158	136	1.7	0.22	<0.10	0.11	1.5				
IHS	99209	C	T2N0M0	19.6	15.3		1.5	0.10	<0.10	0.12					
HDW	99510	T	T2bN0M0	10.8	8.7	NA	1.8	0.41	0.19						
KDJ	99625	C	T3bN0M0	9.8	9.8		0.45	<0.10	<0.10						
MRP	99679	T	T4N0M1	12.2	12.3	NA	0.31	<0.10	<0.10						
KJ	99774	C	T3bN1M0	17.1	17.1		2.1	1.4							
BP	100039	T	T3N0M1	20	31.6	NA	Off study AA only 1.5	0.16							
SCL	100332	C	T2b or ?T2bN1M1	15.4	21.7		9.5								
LDT	101602	T	T3	9.5	MDX 2/1/06										
ECR	101230	T	T3N1M0	7.2	8.4	4.4									
SCJ	101354	C	T2bN1M0	41.0	39.5										

Study arm = C (control) or T (treatment); AA = Androgen ablation

**Screened Study Patients:**

35 patients were screened

14 consented to study

Of the remaining 21 patients:

36% were found to have diffuse mets not meeting the study criteria.

36% had been placed on hormones anywhere from 2 days to years which is a study exclusion.

14% were taking a 5-alpha reductase inhibitor

10% had already undergone a prostatectomy

4% had radiation seed implants